REMARKS

Claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 and 37 are currently pending

Claims 6, 7, 9, 10, 15, 16, 18, 19, 22, 23, 25-29 and 34-36 have been cancelled and the cancellation is without prejudice or waiver.

Claim 37 is currently amended.

Claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 were previously presented.

The following additional remarks addresses all of the Examiners objections and rejections in the same sequence as outlined in the outstanding office action.

PRIORITY

Regarding the priority, it is respectfully submitted that the Examiner please review the prosecution of the earlier application wherein the US Patent Office granted priority back to the grandparent application U.S. 09/017,412. Examiner Polanuri Padmashri and her supervisor Examiner Wang granted the priority during the prosecution of the 09/603,885 application. The Examiner is urged to review the prosecution history of the '885 application which matured into U.S. Patent No. 6,897,017.

The Examiner states that "This application appears to be a CON of U.S. Patent Application Nos. 09/603,885 (filed 6/26/2000), which is now a US Patent, 6,897,017(5/24/2005). The US PATENT, 6,897,017 is a CIP of US Patent Application Nos. 09/017,412 (filed 2/02/1998), which is now a US PATENT, 6,270,964 (8/7/2001). This application also claims priority to U.S. Provisional Application Nos. 60/141,210, filed 6/26/1999."

The word "appears" is not correct nor proper. This application ***"is"*** a Continuation... as recited above.

Furthermore, Applicant's will address now in exquisite detail all the Examiner's issues with the issue of priority as to whether Applicant has complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 35 U.S.C. 120, 121, or 365(c).

Applicant's submit, that the instant CIP application finds support in the grandparent application now U.S. Patent No. 6,270,964 as this later-filed application is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure in the grandparent application and in the later-filed application was sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112.

Applicant respectfully submits ***in toto***, that the disclosure of the prior-filed applications, Application Nos. 09/603,885 and 09/017,412 provide adequate support or enablement for the fluorescent protein reporter in the manner provided by the first paragraph of 35 U.S.C.112 for one or more claims of this CIP application.

The Examiner is correct in stating that the present application claims methods for identifying an interacting set of molecules using green fluorescent protein or mutants thereof as reporter molecules. However, ***Applicant is correct*** in support of the priority because the GFP species is indeed disclosed in the grandparent application (09/017,412) which the parent US Application No.09/603,885 claims the benefit thereof. Therefore, the Applicant is entitled to that embodiment as of the filing date of the grandparent. The US Application 09/603,885 used DHFR as the reporter enzyme as a representative and not a limiting example of the utility of the protein complementation assay technology (hereinafter PCA). Therefore, the parent application because of

its priority to US. 09/017,412 indeed does provide support for the instant claimed method of using a fluorescent protein as a reporter molecule.

The Examiner is correct in that the '885 application claims priority benefit to the grandparent application (09/017,412); filed on 2/2/1998; now patented as US 6,270,964). The Examiner ***is not correct*** in stating that the priority document does not provide adequate support for the claimed methods of identifying an interacting set of proteins using green fluorescent protein (or broadly using fluorescent protein) or mutants thereof.

The Examiner's attention is directed to the '964 patent which has several claims granted by the US Patent office claiming the fluorescent embodiment which the Examiner insists is not supported. For example claim 38 read as follows:

38. *A method for detecting biomolecular interactions said method comprising:*

(a) selecting an appropriate reporter molecule selected from the group consisting of a multimeric enzyme, ***a fluorescent protein****, a luminescent protein and a phosphorescent protein;*

(b) effecting fragmentation of said reporter molecule such that said fragmentation results in reversible loss of reporter function;

(c) fusing or attaching fragments of said reporter molecule separately to other molecules; followed by

(d) reassociation of said reporter fragments through interactions of the molecules that are fused to said fragments; and

(e) detecting said biomolecular interactions by reconstitution of activity of the reporter molecule.

To further show that the fluorescent embodiment was in effect supported by the 09/017,412 application, the Examiners attention is directed to U.S. Patent 7,166,424 which is owned by the same assignee of the present invention and which claims the benefit of the '964 patent. The '424 patent is a CIP of the'424 patent. The priority benefit reads as follows:

This application claims the priority benefit under 35 U.S.C. section 119 of U.S. Provisional Patent Application No. 60/461,133 entitled "Fragments of Fluorescent Proteins for Protein Fragment Complementation Assays", filed Apr. 9, 2003, which is in its entirety herein incorporated by reference. This Application is also a continuation-in-part of pending U.S. application Ser. No. 10/353,090 filed Jan. 29, 2003; which application is a continuation of pending U.S. application Ser. No. 10/154,758 filed May 24, 2002 now U.S. Pat. No. 6,929,916; which is a continuation of U.S. Ser. No. 09/499,464 filed Feb. 7, 2000; and now U.S. Pat. No. 6,428,951; which is a continuation of U.S. Ser. No. 09/017,412 filed Feb. 2, 1998; and now U.S. Pat. No. 6,270,964.

Claim 1 of the '424 patent read as follows:

1. A composition comprising complementary fragments of a fluorescent protein, said fragments generating a fluorescent detectable signal when associated.

Claim 8 of the '424 patent reads as follows:

8. A method for detecting biomolecular interactions said method comprising: (a) selecting an appropriate fluorescent detectable protein; (b) effecting fragmentation of said fluorescent detectable protein such that said fragmentation results in reversible loss of protein function; (c) fusing or attaching fragments of said fluorescent detectable protein separately to

other molecules; (d) reassociating said protein fragments through interactions of the molecules that are fused or attached to said fragments; and (e) detecting the resulting fluorescence signal.

Clearly, those claims were allowed and granted as a patent in view of the publication by Ghosh et al. Antiparallel Leucine Zipper-Directed Protein Reassembly: Application to the Green Fluorescent Protein. *J. Am. Chem Soc.* **vol. 122**, pp. 5658-5659 (2000) which was cited by examiner. The Gosh, et al publication is the basis of the Hamilton publication which the Examiner used in 102(b) rejection (See further below). Clearly, Examiner John Brusca (by the way probably the best patent examiner in the biotech art units) believed that the Green Fluorescent Protein embodiment was enabled by the disclosure of in the 09/017,412 application now U.S. patent No. 6,270,964.

Equity and fairness requires that the patent office provide consistency in how it views and awards claims to priority. Two Examiners (Padmashri Polanuri granting priority to the '964 patent in the '885 case and John Brusca granting priority too to the '424 patent) decision on priority has to be construed as consistent and clearly supported by the original disclosures.

In the office action, the Examiner states that "The relevant passages in the'412 application is a prophetic discussion of the possibility of using GFP." Then it goes on to state that at cols. 23-24 of the '964 patent (parent of the '412 application), the passage recites "Recently the structure of GFP has been solved by two groups, making it now a candidate for a structure-based PCA-design, which we have begun to develop" ('964 patent, col.24, lines 13+)."

The issue is not an issue of prophetic possibility. The issue is ***"Is the inventor in possession of the invention in his creative thoughts of how to use GFP and generate fragments for use in the protein complementation assay and how it would work and will it work"***

Clearly, it has been shown by the Applicant himself by filing CIP's as well as all the copycats (much later filing dates than Applicant's priority date) such as those mentioned in the 35 USC 102 and 103 rejections below that the ***vision of inventor Michnick in selecting fluorescent proteins as reporters has been proven correct.***

Furthermore, the Examiner ***is not correct*** that the applicants have not, at the time of filing of the '964 patent, developed the specific structures for the fragmented GFP (or mutants thereof), or fluorescent protein in general that can be reconstituted for the purpose of detecting protein-protein interactions. The recitation of using GFP (or mutants) or fluorescent protein (or mutants) in general in the '964 patent is not prophetic in nature as the Examiner maintains. The Applicants' indeed, were in possession of the claimed methods of using GFP and broadly using fluorescent protein in general or mutants thereof for the following additional reasons set forth below and for the benefit of the Examiner:

(1) As shown in the parent U.S. patent No. 6,270,964; in particular cols. 3and 4 there is a complete description of how to design a PCA and how to select reporter proteins and enzymes. Starting in col. 3, line 58 and ending in col. 5, line 64, there is ample enablement on how to design protein reporters. Several paragraphs are quoted below:

"One particular strategy for designing a protein complementation assay (PCA) is based on

using the following characteristics: 1) A protein or enzyme that is relatively small and monomeric, 2) for which there is a large literature of structural and functional information, 3) for which simple assays exist for the reconstitution of the protein or activity of the enzyme, both in vivo and in vitro, and 4) for which overexpression in eukaryotic and prokaryotic cells has been demonstrated. If these criteria are met, the structure of the enzyme is used to decide the best position in the polypeptide chain to split the gene in two, based on the following criteria: 1) The fragments should result in subdomains of continuous polypeptide; that is, the resulting fragments will not disrupt the subdomain structure of the protein, 2) the catalytic and cofactor binding sites should all be contained in one fragment, and 3) resulting new N- and C-termini should be on the same face of the protein to avoid the need for long peptide linkers and allow for studies of orientation-dependence of protein binding.

It should be understood that the above mentioned criteria do not all need to be satisfied for a proper working of the present invention. It is an advantage that the enzyme be small, preferably between 10-40 kDa. Although monomeric enzymes are preferred, multimeric enzymes can also be envisaged as within the scope of the present invention. The dimeric protein tyrosinase can be used in the instant assay. The information on the structure of the enzyme provides an additional advantage in designing the PCA, but is not necessary. Indeed, an additional strategy, to develop PCAs is presented, based on a combination of exonuclease digestion-generated protein fragements followed by directed protein evolution in application to the enzyme aminoglycoside kinase. Although the overexpression in prokaryotic cells is preferred it is not a necessity. It will be understood to the skilled artisan that the enzyme catalytic site (of the chosen enzyme) does not absolutely need to be on same molecule.

The present application explains the rationale and criteria for using a particular enzyme in a PCA. FIG. 1 shows a general description of a PCA. The gene for a protein or enzyme is rationally dissected into two or more fragments. Using molecular biology techniques, the chosen fragments are subcloned, and to the 5' ends of each, proteins that either are known or thought to interact are fused. Co-transfection or transformation these DNA constructs into cells is then carried out. Reassembly of the probe protein or enzyme from its fragments is catalyzed by the binding of the test proteins to each other, and reconstitution is observed with some assay. It is crucial to understand that these assays will only work if the fused, interacting proteins catalyze the reassembly of the enzyme. That is, observation of reconstituted enzyme activity must be a measure of the interaction of the fused proteins."

(2) As shown starting in col. 23, line 65 to col. 24, line 22 of the parent U.S. patent No. 6,270,964; regarding the fluorescent protein embodiment, Applicant quotes the entire paragraph:

"GFP from Aequorea victoria is becoming one of the most popular protein markers for gene expression. This is because the small, monomeric 238 amino-acids protein is intrinsically fluorescent due to the presence of an internal chromophore that results from the autocatalytic cyclization of the polypeptide backbone between residues Ser65 and Gly67 and oxidation of the--bond of Tyr66. The GFP chromophore absorbs light optimally at 395 nm and possesses also a second absorption maximum at 470 nm. This bi-specific absorption suggests the existence of two low energy conformers of the chromophore whose relative population depends on local environment of the chromophore. A mutant Ser65Thr that eliminates isomerization (single

absorption maximum at 488 nm) results in a 4 to 6 times more intense fluorescence than the wild type. Recently the structure of GFP has been solved by two groups, making it now a candidate for a strucutre-based PCA-design, ***which we have begun to develop****. As with the GST assay, we are doing all of our initial development in E. coli with GCN4 leucine zipper-forming sequences as oligomerization domains. Direct detection of fluorescence by visual observation under broad spectrum UV light will be used. We will also test this system in COS cells, selecting for co-transfectants using fluorescence activated cell sorting (FACS)."*

Note also references 152 – 159 (incorporated by reference in the '264 grandparent application) at cols. 42 and 43 which are reproduced below:

152. Chalfie, M., Tu, Y., Euskirchen, G., Ward, W. W. & Prasher, D. C., Green fluorescent protein as a marker for gene expression. *Science* 263, 802-5 (1994).

153. Cody, C. W., Prasher, D. C., Westler, W. M., Prendergast, F. G. & Ward, W. W.:Chemical structure of the hexapeptide chromophore of the Aequorea greeN-fluorescent protein. *Biochemistry* 32, 1212-8 (1993).

154. Morin, J. G. & Hastings, J. W.:Energy transfer in a bioluminescent system. Journal of *Cellular Physiology* 77, 313-8 (1971).

155. Morise, H., Shimomura, O., Johnson, F. H. & Winant, J.:Intermolecular energy transfer in the bioluminescent system of Aequorea. *Biochemistry* 13, 2656-62 (1974).

156. Ward, W. W. & Bokman, S. H.:Reversible denaturation of Aequorea greeN-fluorescent protein: physical separation and characterization of the renatured protein. *Biochemistry* 21, 4535-40 (1982).

157. Heim, R., Prasher, D. C. & Tsien, R. Y.:Wavelength mutations and posttranslational autoxidation of green fluorescent protein. *Proc. Nati. Acad. Sci.* USA 91, 12501-4 (1994).

158. Ormo, M., Cubitt, A. B., Kallio, K., Gross, L. A., Tsien, R. Y. & Remington, S. J.:Crystal structure of the aequorea victoria green fluorescent protein. *Science* 273, 1392-1395 (1996).

159. Youvan, D. C. & Michelbeyerle, M. E.:Structure and fluorescence mechanism of gfp. *Nature Biotechnology* 14, 1219-1220 (1996).

Clearly, all of the above prior publications show what was known about GFP at the time of the invention of PCA resulted in the Applicant "inventive genius" that GFP is indeed a protein reporter that would work which have been conclusively proven as shown in the instant application as well as other CIP applications by the inventor such as the '424 patent.

Since the description in the grandparent case (the '964 patent) is fully supported for the GFP embodiment, Applicant is entitled to the priority going back to the '964 patent. The CCPA (now the CAFC) set the record straight in 1970, where it stated that the number and variety of examples is

irrelevant if the disclosure is "enabling" and sets forth the "best mode contemplated". *In re Borkowski et al.* (CCPA 1970) 442 F2d 904, 164 USPQ 642.

Furthermore, there is no absolute statutory requirement that every embodiment or for that matter a single embodiment be exemplified if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski et al.* (CCPA 1970) 442 F2d 904, 164 USPQ 642.

Additionally, use of prophetic language or examples does not automatically make a patent non-enabling merely because there can be no guarantee that the examples would actually work. *Atlas powder Co. v. E.I. DuPont de Nemours & Co.* (CAFC 1984) 750 F2d 1569, 224 USPQ 409.

Furthermore, as explained further below under the 35 USC 102 and 103 rejections, the inventors of the references used by the Examiner to issue the rejections namely Umezawa, et al. and Hamilton, et al. were the recipients of poster presentations by Dr. Michnick's presentations on PCA where he discussed the many protein reporters he envisioned as working reporters including fluorescent proteins.

CLAIM OBJECTIONS

The objection to claim 37 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim has been addressed by amending the claim to remove the dependency from claim 14. Accordingly, withdrawal of this objection is respectfully requested.

WITHDRAWAL OF CLAIM REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

The withdrawal of the rejection of claims 1-5, 8, 11-14, 17, 20, 21, 24, 30-33 and 37 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is acknowledged with appreciation.

THE CLAIM REJECTIONS UNDER 35 USC § 102

Umezawa et al

Claims 1-3, 8, 11-13, 17, 20, 21, 24 and 30-33 stand rejected under 35 U.S.C. § 102(a) and102(b) as being anticipated by Umezawa et al (PCT/JP00/09348; WO 02/08766; 1/31/02; or the english equivalent, US 20030003506 (a 371 of PCT/JP00/09348). Withdrawal of this rejection is courteously requested.

The Umezawa reference has limitations and can not be construed as being a PCA as contemplated by the instant invention. Note that the Umezawa et al. method requires that the constructs used be a fusion polypeptide wherein the carboxyl terminus of an N-terminal portion of an indicator protein is fused to the N-terminus of the N-terminal portion of ***an intein polypeptide*** (protein splicing element) and that in carrying out their assay a "portion of the intein are sufficient to effect trans-splicing, and wherein the N-terminal portion of the indicator protein and the C-terminal portion of the indicator protein constitute a functioning indicator protein after ***intein mediated trans-splicing occurs***."

Clearly, the Umezawa, et al. reference is not applicable to the method claims of the instant invention. In any event, notwithstanding the differences enumerated above, Applicant believes that the Umezawa et al. reference is not applicable under 35 USC 102(b) or 102(a) because Applicant's

priority date is more than a year prior to the filing of Umezawa invention. Applicant's priority date is February 2, 1998, (January 31, 1997 going back to the Canadian priority) while Umezawa's priority date is July 26, 2000 based on foreign priority.

Once again, it is reiterated that Umezawa et al. is not the same invention and that the requirement of intein mediated trans splicing distinguishes away from applicant's PCA assays.

Hamilton et al and Hamilton '599

Claims 1-5, 8, 11-14, 17, 20, 21, 24, and 30-33 stand rejected under 35 U.S.C. § 102(b) and § 102(e) as being anticipated by Hamilton et al (US 2002/0146701; 10/10/2002) and (US 6,780,599; 8/24/2004; filed 5/14/2001; priority date 5/12/2000) respectively.

Since the priority date of the Hamilton et al. application and patent is more than two subsequent to Applicant's priority date, it is well established tenet of our patent laws that those two citations are not applicable references.

Once again, Applicant respectfully submits that the Hamilton et al and Hamilton '599 references are not applicable because Applicant's priority record clearly beats the Hamilton filing by more than one year and the further evidence of the CIP patent US 7,166,424 beats the Hamilton patent on priority and therefore establishes a clear dominant position of Applicant's prior conception because Applicant's filing date is much earlier than Hamilton, et al. The U.S. Patent Office granted our '424 patent, because it recognized that our priority position precedes any filing by Hamilton, et al.

Once again, Applicant reiterates that Umezawa, et al. and Hamilton, et al. were both recipient of seminar lectures given by Dr. Michnick at their institutions. Of course, Applicant had

already filed their application in Canada and in the US where the fluorescent embodiment was disclosed.

There is no doubt that Applicant's priority in the technology has been well established.

THE CLAIM REJECTIONS UNDER 35 USC § 103

Claims 1-5, 8, 11-14, 17, 20, 21, 24 and 30-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Umezawa et al (PCT/JP00/09348; WO 02/08766; 1/31/02 or the English equivalent US 20030003506), in view of Hamilton et al (US 2002/0146701; 10/10/2002). Withdrawal of the rejection is respectfully requested.

Since Applicant's firmly believes that their priority date is at least two years prior to both references of record, it is respectfully submitted that the combination rejection as applied by the examiner is not relevant since Applicant's invention date is prior to the dates of those two references.

SUMMARY AND CONCLUSION

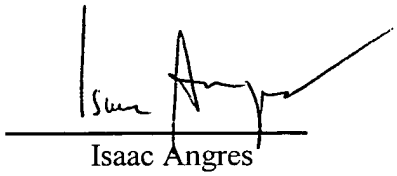
Entry and consideration of the present amendment, reconsideration of the outstanding office action, and allowance of the present application and all of the claims therein are respectfully requested and now believed to be appropriate.

Any amendment to the claims that have been made in this amendment, which do not narrow the scope of the claims, and which have not been specifically noted to overcome a rejection based upon the prior art, should be considered cosmetic in nature, and to have made for a purpose unrelated to patentability, and no estoppel should be deemed to attach thereto.

In view of the above amendments and remarks, it is respectfully submitted that the claims are now in condition for allowance. The Examiner is invited to contact the undersigned at 703-418-2777 if he/she feels that further discussion may facilitate the resolution of any outstanding issues.

An early indication of a Notice of Allowance is earnestly solicited.

Respectfully submitted,



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